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STRUCTURE AND BIOLOGICAL ACTIVITY OF THE FURAN-DITERPENOIDS FROM THE GENERA *LEONOTIS* AND *LEONURUS*

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Abstract – The present review, covering the literature up to 2006, reports the chemistry and the biological activities of the diterpenoids occurring in the aerial parts of species belonging to the genera *Leonotis* and *Leonurus*, family Lamiaceae.

Leonotis and *Leonurus*, family Lamiaceae (Labiatae), tribe Stachyoideae, are two small genera, including about forty and eighty species respectively.[1]

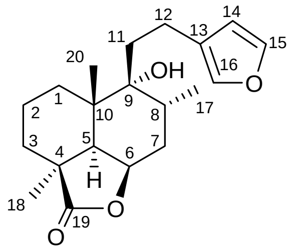
During the last sixty years, several species were investigated for the search of diterpenoids. The present review is an updated report on the researches on this class of natural products isolated from these genera.

Concerning the genus *Leonotis*, it occurs in the tropical belt: Caribbean Islands, South America, India, Africa (specially South Africa). Indeed, a large contribution to the investigations on this genus was given by SouthAfrican researchers.

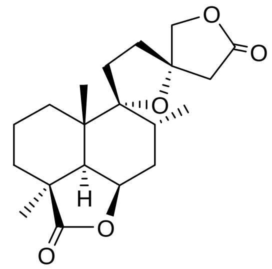
The first results on the chemistry of the diterpenes from the genus *Leonotis* appeared in 1962:[2] two products were isolated from the aerial parts of *Leonotis leonurus* R. Br. collected in South Africa and provisionally indicated as compound X and compound Y. Two years later the extraction of the same species yielded[3] the well known marrubiin, previously isolated from *Marrubium vulgare* L. and whose labdanic structure **1** had been elucidated just in those years after one century of investigations. The compounds X and Y were isolated again, and their structures were elucidated some years later[4] as **2** and **3** respectively: the labdane skeleton and some details of the functional groups clearly indicate that they are closely related to marrubiin, and are new natural products.

The structure **2** of compound X was also confirmed by X-ray analysis.[5] In a paper concerning diterpenoids from a *Solidago* (Compositae),[6] the structure of compound Y was proved to be correct by formal total synthesis starting by a derivative of marrubiin.

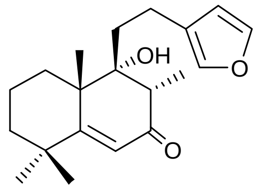
This paper is dedicated to Professor Dr. Ekkehard Winterfeldt on the occasion of his 75th birthday



1 marrubiin



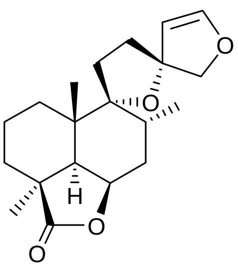
2 compound X



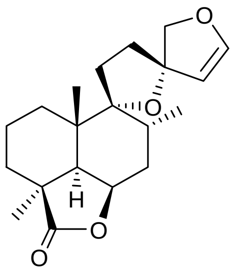
3 compound Y

Some years after, the two stereoisomeric premarrubiins (**4**) (13*R*) and (**5**) (13*S*) were also isolated[7] from the same species on a sample collected in Italy: no other diterpenes were detected.

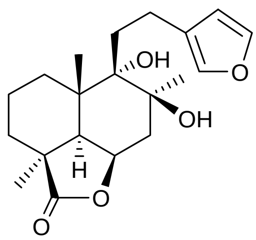
A species particularly rich in diterpenoids is *Leonotis nepetaefolia* R. Br. In 1969 a new product, leonotin, was isolated[8] and proved to have the structure **6** of 8β-hydroxy-marrubiin. The same substance was found in *Leonotis leonitis* R. Br.[9] and in *Leonotis dysophylla* Benth.[10]



4 13*R*-premarrubiin

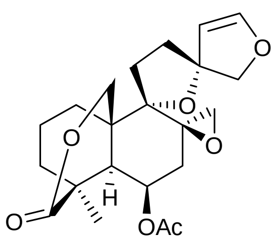


5 13*S*-premarrubiin

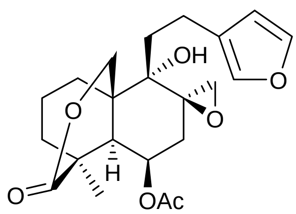


6 leonotin

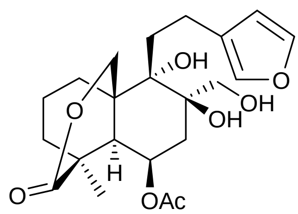
Continuing the investigations on *Leonotis nepetaefolia*, other diterpenoids were found. Nepetaefolin (**7**) is a new prefuranic compound, characterized by the occurrence of an 8,17-epoxide and a 18,20-lactone.[11,12] Its structure was confirmed by X-ray analysis[13] In the previous paper[12] two new products were reported, nepetaefuran (**8**) and nepetaefuranol (**9**). The former is the product of furanization of nepetaefolin, whereas in the latter the 8,17-epoxide has changed into a 8β,17-diol.



7 napetaefolin



8 napetaefuran

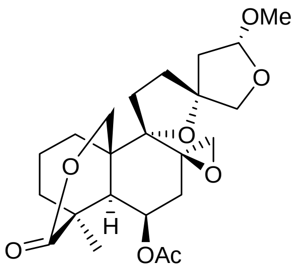


9 napetaefuranol

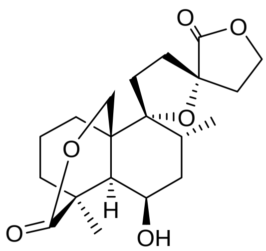
Always from *Leonotis nepetaefolia* another compound was isolated,[14] methoxynepetaefolin (**10**): it is the product of formal addition of MeOH on the 14,15 double bond of nepetaefolin; its structure was confirmed by X-ray crystallographic analysis.[15]

Three more diterpenoids were found[16] in *Leonotis nepetaefolia*: nepetaefolinol (**11**), leonotinin (**12**) and the dilactone (**13**); the last two products show the 19,20-lactone group. Also the structure of nepetaefolinol was confirmed by X-ray analysis.[15]

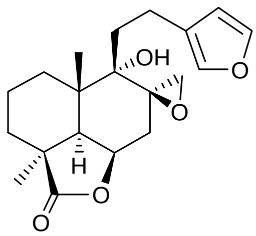
Many years after, a paper[17] reported further investigations on *L. nepetaefolia*: besides the already known nepetaefolinol (**11**), two more natural diterpenoids were isolated. The first is the product of dehydratation of nepetaefolinol, resulting in the forming of a 5,6 double bond (dehydronepetaefolinol, **14**), the last is a furanic tetrol (**15**) (no trivial name given) indicated as 15,16-epoxy-labda-13(16),14-diene-6β,9,17,19-tetrol, arising from the reduction of leonotinin (**12**). The structures were established by X-ray analysis.



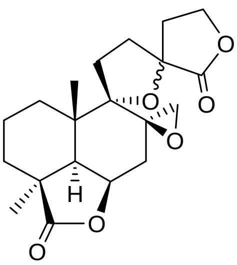
10 methoxynepetaefolin



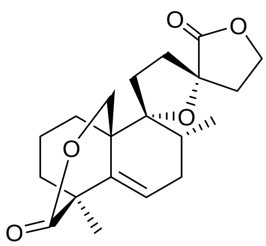
11 napetaefolinol



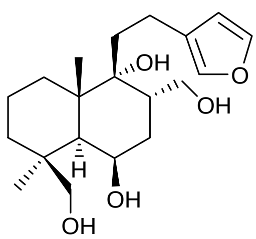
12 leonotinin



13 dilactone



14 dehydro-nepetaefolinol



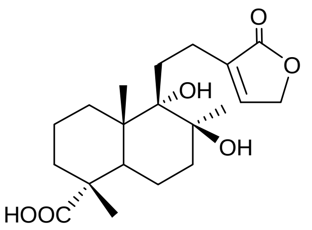
15

The most recent study on *Leonotis nepetaefolia*[18] led to isolation of a new labdane diterpene, leonotinic acid (**16**). The 4α equatorial carboxyl group is quite unusual.

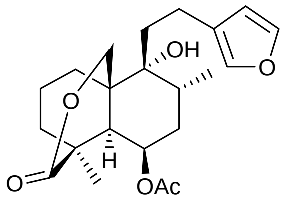
Another species, *Leonotis dubia* E. Mey, now classified as *L. ocymifolia* var. *ocymifolia*, yielded[19] the furolabdane dubiin (**17**): characteristics are the 9α-hydroxy group and the 19,20-lactone. The structure and absolute stereochemistry were confirmed[20] by X-ray and CD determinations.

The species *Leonotis leonitis* R. Br. contained[21] the dilactone leonitin (**18**), in which the occurrence of the 20-acetoxy group is remarkable. The product is quite similar to product X (**2**), from which differs for having the carbon atom 20 as a CH_2OAc group instead of CH_3. The complete stereochemistry of leonitin as **18** was ascertained by X-ray analysis.[22] The occurrence also of leonotin (**6**) in this species had been signalled in an old communication.[9]

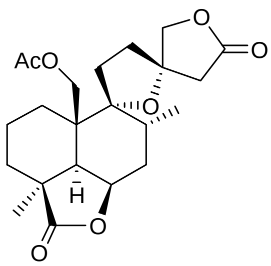
From the species *Leonotis leonitis* var. *hirtiflora* (Benth.) Skan another diterpenoid was isolated[23] and elucidated as 9α,13(*S*)-epoxy-8β-hydroxylabdane-6β,19;16,15-diolide (**19**) (no trivial name given).



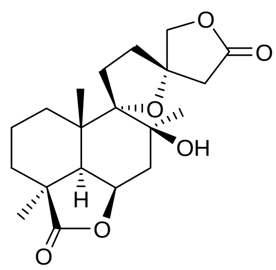
16 leonotinic acid



17 dubiin



18 leonitin



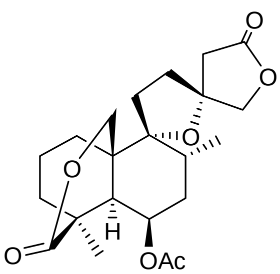
19

Finally, from the species *Leonotis ocymifolia* (Burm. f) Iwarsson var. *raineriana* (Visiani) Iwarsson four products were isolated:[24] the already known leonitin (**18**) and compound X (**2**), and two new diterpenic natural products. The first is the dilactone (**20**), 6β-acetoxy-9α,13α-epoxylabda-20(19),16(15)-diol-dilactone. The second was assigned the structure **21**, 20-acetoxy-9α,13-dihydroxy-15(16)-epoxylabd-14-en-6β(19)-lactone (no trivial names given to both products).

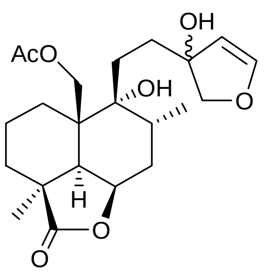
A recent paper[25] re-examined the same plant and showed the occurrence of leonotin (**6**), leonotinin (**12**) and nepetaefolin (**7**). The paper reported also the complete NMR data of these three diterpenoids and of six related diterpenoidic compounds.

Several informations on the researches in progress in 1983 had been reviewed by Rivett in a lecture.[26]

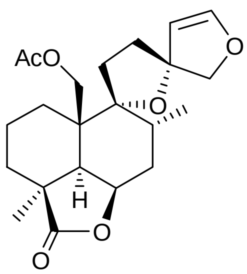
Quite recently,[27] from a new sample of *Leonotis leonurus* a new labdane diterpenoid, leonurun (**22**) was isolated in South Africa. Its structure differs from 13*R*-premarrubiin **4** only for having C-20 as CH_2-O-CO-CH_3 instead as CH_3.



20 dilactone



21 lactone



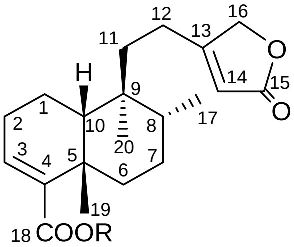
22 leonurun

In total, from the genus *Leonotis* 22 diterpenoids have been isolated: of them, 19 are new natural products whereas three (**1**, **4**, **5**) were already known as occurring in *Marrubium vulgare* L. The labdane skeleton is present in all these diterpenoids, and is therefore a marker of the genus. The fourth isoprenic unit is always in the form of an oxigenated pentatomic ring, as a furan, prefuran, saturated or unsaturated γ-lactone system. The occurrence of 19,6 or 18,20 lactones is frequent (nineteen out of twenty-two). It is remarkable that only few species of the genus have been investigated.

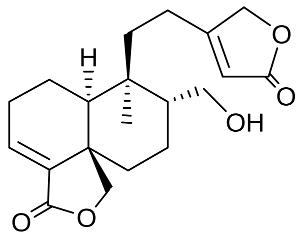
The genus *Leonurus* is widespread in Eurasia, from Western Europe to China.

The first paper on the chemistry of terpenoids from this genus was published in 1972: it reported the occurrence of several products, probably bicyclic diterpenoids with furan and lactone groups[28] in *Leonurus cardiaca* L. Their structures were not identified.

In 1973 a paper reported[29] the isolation of two new products from *Leonurus marrubiastrum* L., marrubiaside and marrubialactone. Their structures were elucidated by classical chemical degradation and spectroscopic investigations. Marrubiaside (**23**) is the β-D-glucopyranosyl derivative of the aglycone marrubiagenin (**24**): the last was obtained by acid or enzymatic hydrolysis. Marrubialactone is represented by structure **25**. Both products show an oxidized furan ring forming an unsaturated γ-lactone system. Such structures are worthy of an important remark: whereas all the diterpenoids occurring in *Leonotis* do show a labdane backbone, on the contrary, these two products isolated from *Leonurus marrubiastrum* have a labdane-rearranged skeleton; this result indicates a certain difference from the quite similar *Leonotis* genus; moreover, the occurrence of a glycosidic product is rather rare in these genera.



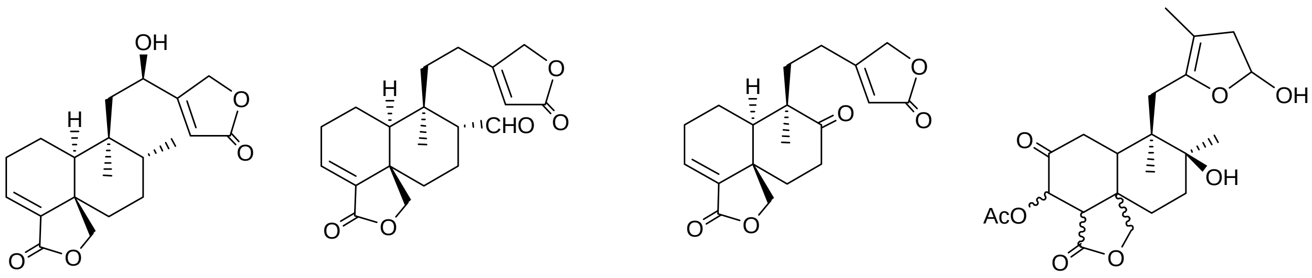
23 R = β-D-Glu marrubiaside
24 R = H marrubiagenin



25 marrubialactone

Five years later, a reinvestigation of *Leonurus marrubiastrum* led to the isolation of three new products, again with the rearranged labdane skeleton:[30] marrubiastrol (**26**), aldehydo-marrubialactone (**27**) and desmethylmarrubiaketone (**28**). Also in these products the oxidized furan ring occurs. The norditerpene (**28**) is also remarkable for the loss of C-17. In the original paper the indication of some carbon atoms is different from the usual numbering.

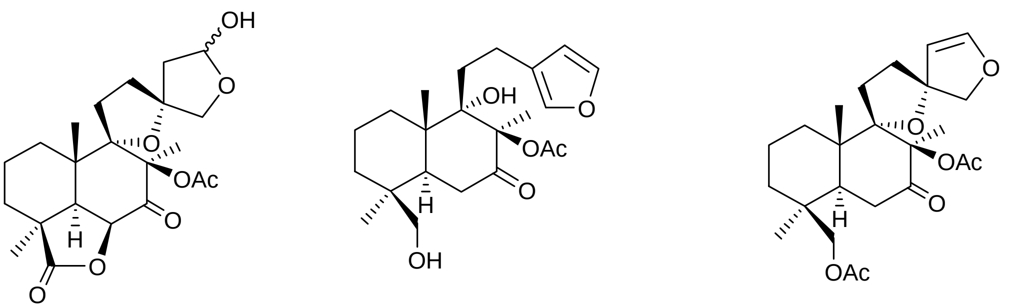
The investigation of *Leonurus cardiaca* L. was taken again[31] by the first group: one of the products previously isolated[28] was identified as a new derivative, indicated as “clerodane B”, and formed by a mixture of two epimers, maybe at C-4 and C-5. In the provisional structure **29** the configurations at C-3, C-4 and C-5 were not elucidated; no other papers on this substance appeared later.



26 marrubiastrol **27** aldehydomarrubialactone **28** desmethylmarrubiaketone **29** "clerodane B"

Some years after, other authors[32] reported the isolation of leocardin, an epimeric mixture at C-15, from *Leonurus cardiaca*: the structure **30** was firmly ascertained. No other products were found. It is very interesting to note that leocardin has the labdane skeleton.

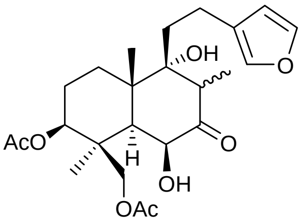
Only many years after, a new labdane diterpenoid, 19-hydroxygaleopsin (**31**) was found in *Leonurus cardiaca*.[33] A labdane prefuranic compound, 19-acetoxypregaleopsin (**32**) was isolated from the same species.[34]



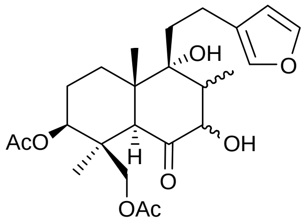
30 leocardin **31** 19-hydroxy-galeopsin **32** 19-acetoxy-pregaleopsin

Another species, *Leonurus sibiricus* L., yielded three new labdane derivatives:[35] leosibirin (**33**), isoleosibirin (**34**) and leosibiricin (**35**). The first and second product have the typical furano-labdanic structure, while the third is a prefuranic derivative.

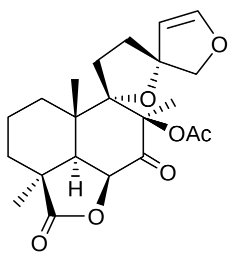
A paper[36] concerning the accumulation of furanic labdanes in *Leonurus cardiaca* in different stages of its growth reported the occurrence of leosibiricin (**35**) as the major component of the diterpenic fraction: this labdane had been previously isolated from *Leonurus sibiricus*.[35] The same paper[36] proved that the labdanes occur only in the aerial part of the plant. Further investigations are desirable to ascertain which diterpenoids really occur in the samples of *L. cardiaca* collected in different geographical areas.[28, 31-34, 36]



33 leosibirin



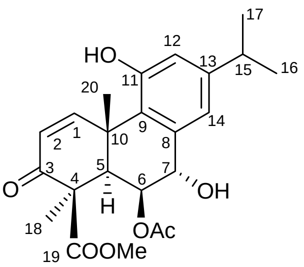
34 isoleosibirin



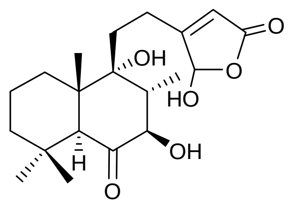
35 leosibiricin

Coming back to *Leonurus marrubiastrum*, a more recent paper[37] reported the isolation of an abietane diterpenoid, leonubiastrin (**36**). The occurrence of another skeleton, quite different from labdane and rearranged labdane, is rather singular and could put some questions about the taxonomy of the genus *Leonurus*.

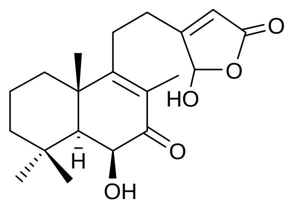
Quite recently, seven new labdane diterpenes were isolated[38] from *Leonurus sibiricus*: sibiricinone A (**37**), sibiricinone B (**38**), sibiricinone C **(39)**, sibiricinone D (**40**), sibiricinone E (**41**), 15-*epi*-sibiricinone D (**42**) and 15-*epi*-sibiricinone E (**43**). In all the products the oxidized furanic system occur. It is remarkable that products **39, 40, 41, 42, 43** have a 15-OCH_3 substituent; **40** and **41** are a C-15 epimeric pair with 13*R* configuration, while **42** and **43** are a C-15 epimeric pair with 13*S* configuration.



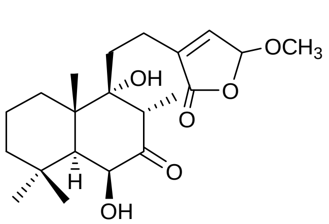
36 leonubiastrin



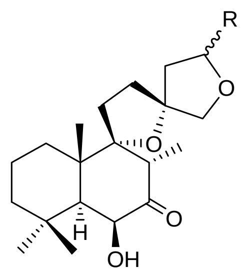
37 sibiricinone A



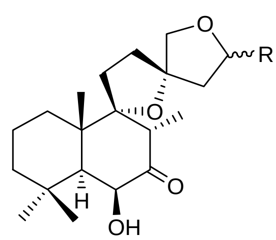
38 sibiricinone B



39 sibiricinone C



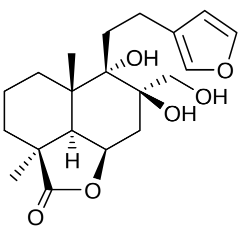
40 R = αOCH_3 sibiricinone D
41 R = βOCH_3 *epi*-sibiricinone D



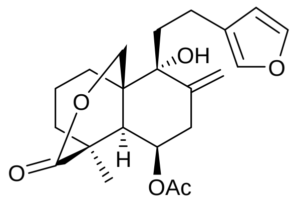
42 R = αOCH_3 sibiricinone E
43 R = βOCH_3 *epi*-sibiricinone E

Another recent paper[39] reported the isolation from *L. sibiricus* of two new furolabdanes, whose structures were elucidated as **44** and **45**; the products were indicated as LS-1 and LS-2 respectively and no trivial names were given. The extract contained also four known diterpenoids, leonotinin **12**,[16] leonotin **6**,[8] dubiin **17**[19] and nepetaefuran **8**.[12] These four products had been isolated from species of the *Leonotis* genus, and not of the *Leonurus* genus, as erroneously indicated in this paper.

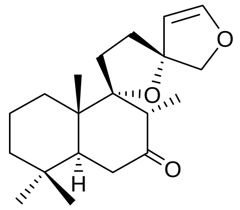
The species *Leonurus heterophyllus* Sweet is rich in furolabdane diterpenoids. A first paper[40] reported the isolation of a new product, prehispanolone (**46**); this prefuranic compound was converted into the known hispanolone (**47**), previously isolated from *Ballota hispanica*[41] and *Galeopsis angustifolia*.[42] In a following investigation, two new compounds were found,[43] leoheterin (**48**) and preleoheterin (**49**), together with the known hispanolone (**47**) and galeopsin (**50**).[42]



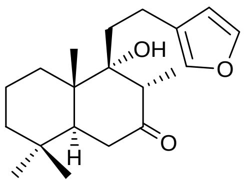
44 LS-1



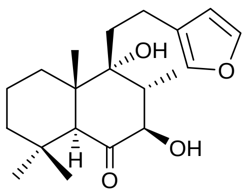
45 LS-2



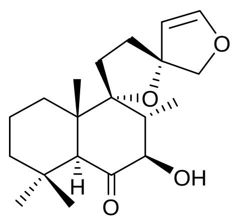
46 prehispanolone



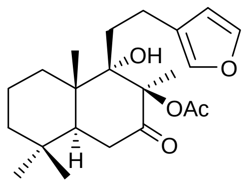
47 hispanolone



48 leoheterin

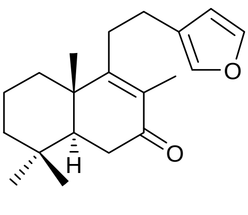


49 preleoheterin

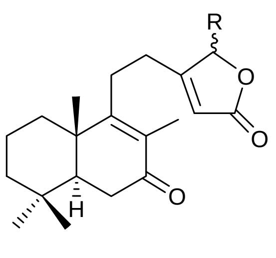


50 galeopsin

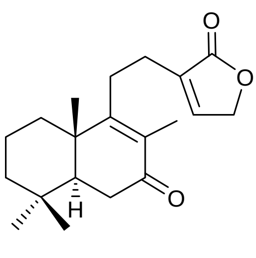
A quite recent paper[44] reported the isolation, together with the previously found compounds, of the known hispanone (**51**) (occurring in *Galeopsis angustifolia*[45]), and of five new furolabdanes: leoheteronin A (**52**), leoheteronin B (**53**), leoheteronin C (**54**), leoheteronin D (**55**) and leoheteronin E (**56**). The synthesis of prehispanolone was reported.[46,47]



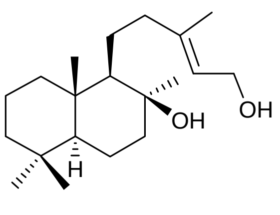
51 hispanone



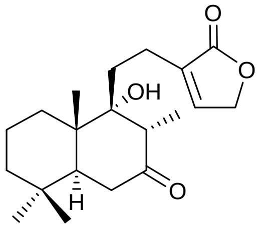
52 R = H leoheteronin A
54 R = OH leoheteronin C



53 leoheteronin B

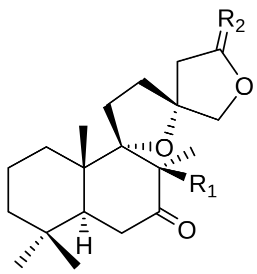


55 leoheteronin D

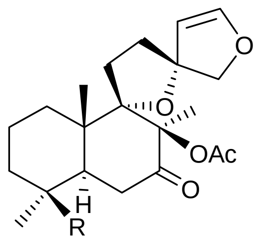


56 leoheteronin E

Also *Leonurus persicus* Boiss. is very rich in diterpenoids. A first paper[48] reported the isolation of five new labdane compounds: leopersin A (**57**), 8-deacetoxyleopersin A (**58**), leopersin B (**59**), 15-*epi*-leopersin B (**60**) and 4β-hydroxymethylpregaleopsin (**61**) (name corrected[49] to 19-hydroxypregaleopsin), together with the known products pregaleopsin **62**,[42] galeopsin (**50**)[42] and leosibiricin (**35**).[35] Improved NMR data of these last three compounds were reported.



57 R_1 = OAc, R_2 = O leopersin A
58 R_1 = OH, R_2 = O 8-deacetoxy-leopersin A
59 R_1 = OAc, R_2 = αH, βOH leopersin B
60 R_1 = OAc, R_2 = βH, αOH 15-*epi*-leopersin B

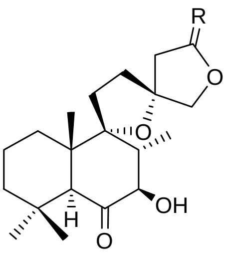
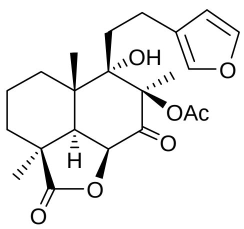
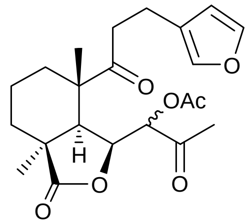


61 R = CH_2OH 19-hydroxypregaleopsin
62 R = CH_3 pregaleopsin

A remark about leosibiricin (**35**): the product isolated in 1995 by Tasdemir et al.[48] was reported to have a negative rotatory power, hypothesizing that it could be the enantiomer of leosibiricin isolated in 1982 by Savona et al.[35] and reported to have a positive rotatory power. Actually, the two products have identical spectroscopic data and are identical. Indeed, an unfortunate misprint in the 1982 paper quoted a positive value instead of the negative value: (+) instead of (-). Therefore leosibiricin is represented by the structure and stereochemistry **35**.

In a second paper[49] the same authors described six new furolabdane derivatives from *L. persicus*: leopersin C (**63**), 15-*epi*-leopersin C (**64**), leopersin D (**65**), leopersin E (**66**), leopersin F (**67**) and 7-*epi*-leopersin F (**68**). The last two products show the interesting structure of 8,9-seco-labdane.

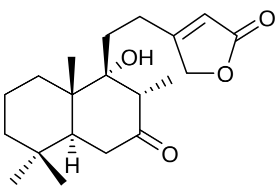
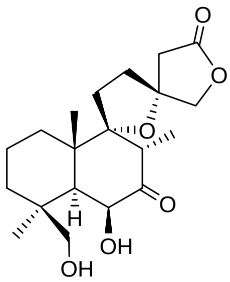
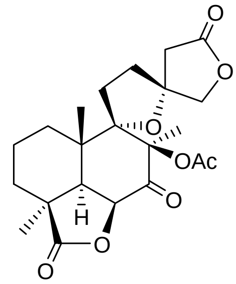
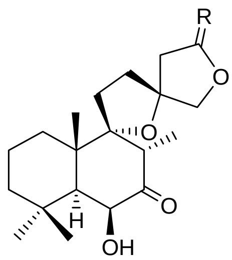
Further labdane diterpenoids were isolated from *L. persicus*.[50] Seven compounds are new: leopersin G (**69**), leopersin H (**70**), leopersin I (**71**), leopersin J (**72**), 15-epi-leopersin J (**73**), leopersin K (**74**), leopersin L (**75**). Also two known diterpenoids occurred: 13-hydroxyballonigrinolide (**76**), previously isolated from *Ballota lanata*[51] and ballotenol (**77**), previously found in *Ballota nigra*.[52] The configuration at C-8 of ballotenol was revised and assigned as 8α-CH_3. These results seem to indicate a close relationship between the genera *Ballota* and *Leonurus*.

63 R = αH, βOH leopersin C
64 R = βH, αOH 15-*epi*- leopersin C
65 R = O leopersin D

66 leopersin E

67 / **68** leopersin F / 7-*epi*-leopersin F

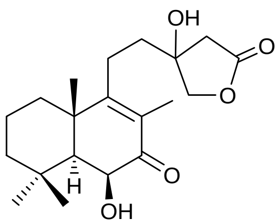
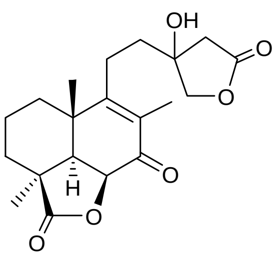
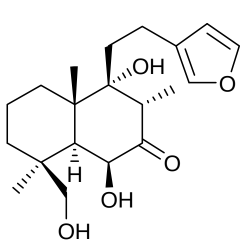





69 leopersin G

70 leopersin H

71 leopersin I

72 R = αH, βOH leopersin J
73 R = βH, αOH 15-*epi*- leopersin J
74 R = O leopersin K

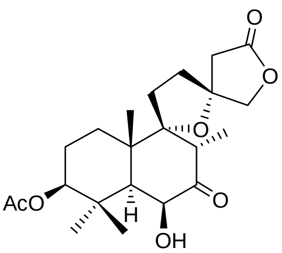
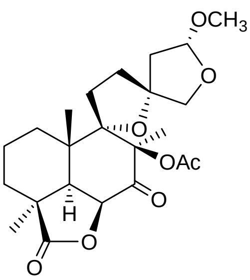
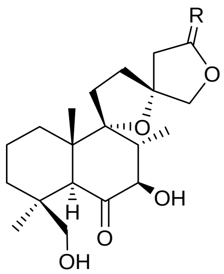
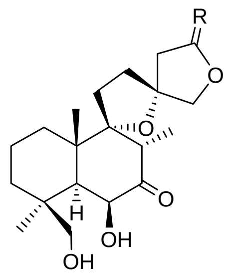




75 lepersin L

76 13-hydroxy-ballonigrinolide

77 ballotenolo

Another paper on *L. persicus*[53] reported seven new diterpenoids: leopersin M (**78**), leopersin N (**79**), leopersin O (**80**), 15-*epi*-leopersin O (**81**), leopersin P (**82**), leopersin Q (**83**), 15-*epi*-leopersin Q (**84**). Also 19-hydroxygaleopsin (**31**) was isolated and described as a new product, but it had been described few months before[33].

78 leopersin M

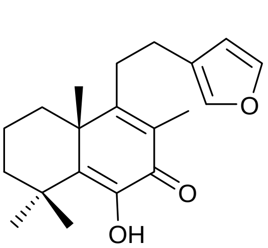
79 leopersin N

80 R = αH, βOH leopersin O
81 R = βH, αOH 15-*epi*- leopersin O
82 R = O leopersin P

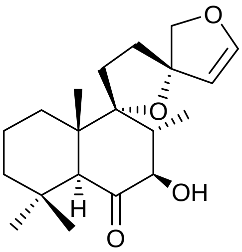
83 R = αH, βOH leopersin Q
84 R = βH, αOH 15-*epi*- leopersin Q

A quite recent paper[54] reported the occurrence of three new labdanes in *L. japonicus* Houtt., considered as synonimous of *L. heterophyllus* Sweet: leojaponin (**85**), 13-*epi*-preleoheterin (**86**), *iso*-preleoheterin (**87**), together with the known preleoheterin (**49**).

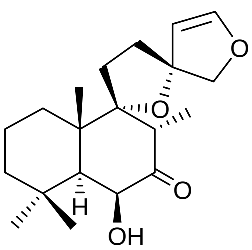
Again from *L. heterophyllus*, two new furolabdane were isolated very recently, and attributed the structures **88** for heteronone A[55, 56, 57] and **89** for heteronone B.[56,57]



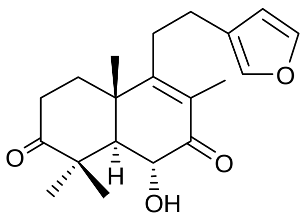
85 leojaponin



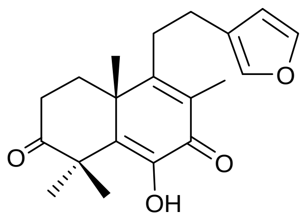
86 13-*epi*-preleoheterin



87 *iso*-preleoheterin



88 heteronone A



89 heteronone B

It is clear that the genus *Leonurus* is much richer in diterpenoids than the genus *Leonoti*s. Indeed, from the only six species investigated until now, a total of 71 products was isolated: 61 of them are new natural products, whereas 10 had been isolated previously from other plants: in particular from species of the genera *Ballota*, *Galeopsis* and *Leonotis*.

As for the taxonomic aspect, the Stachyoideae tribe of the Lamiaceae family contains many genera rich in diterpenoids. Chemotaxonomic results show a certain closeness between the genera *Galeopsis*, *Ballota*, *Marrubium*, *Leonuru*s and *Leonoti*s: indeed the same compound can be found in more than one genus. This is for instance the case of marrubiin occurring in *Marrubium* and *Leonotis*, galeopsin in *Galeopsis* and *Leonurus*, hispanolone in *Ballota*, *Galeopsis* and *Leonurus*, ballotenol in *Leonurus* and *Ballota*. The skeletal structures can be markers to distinguish the genera: in the case of the two genera subject of the present review, it is evident that *Leonotis* contains only labdane derivatives, therefore they are typical of the genus. On the contrary, in *Leonurus* there are mainly diterpenoids with the labdane backbone, but in *L. marrubiastrum* there are also some products with rearranged labdane and abietane skeleta.

Biological activity

A number of informations and results has been reported concerning the biological activities of species belonging to the *Leonotis* and *Leonurus* genera.

Many species were used in folk medicine: this the case of *Leonotis leonurus* in Southern Africa, where it is called "wild dagga"[2] or "wild hemp":[58] it is used as anticonvulsant,[59] antinociceptive, antiinflammatory, antidiabetic,[60] antiarthritic, antidote for snake bite,[58] antibacterial.[61] Aqueous or ethanolic extracts are usually prepared. Effects on prostaglandin-synthesis inhibition[62] and on fibroblast growth stimulation[61] were investigated.

Leonotis dubia is used in Africa against whooping cough.[19] *Leonotis ocymifolia*, Eastern and Southern Africa, is quoted to have ascaricide and anticancer activity and to cure ulcers and wounds;[23] it is also reported to be a narcotic and habit forming drug.[63]

Probably the most used species is *Leonotis nepetaefolia*, in Africa, India, Caribbean countries, South America, that has attributed a variety of salutary physiological effects.[56] It is called "molinillo" in Puerto Rico, "chandelier" in Trinidad, "Christmas candle stick" in Jamaica, "dagga" in Africa. In India it is an ancient Ayurvedic drug.[16] Smoking of dried leaves is a common practice in many countries as a narcotic drug.[14] Folk medicine used extracts as antitumour, antifungal, antimalarial, hypotensive, tonic, laxative, sedative, insecticide, antiviral, antibacteric, to cure coughs, fever, stomach ache, head ache, kidney diseases, rheumatism, dysmenorrhea, asthma, burns. Pharmacological investigations regarded anticancer activity,[64] antibacterial,[65] antifungine.[66] Also the activity on smooth muscle and cardiac muscle was studied.[67] It was ascertained that in Central Mexico *Leonotis nepetaefolia* is a reservoir for several viruses.[68]

Also the species of *Leonurus* are reported to have interesting biological activities and a very large use in folk medicine, specially in China. The most used species are *L. japonicus* (syn. *L. heterophyllus*, *L. artemisia*) and *L. sibiricus*. There are many hundreds Chinese patents for commercial preparations, usually in mixtures with other plants or animal parts: such preparations are claimed to be active against any human or animal disease. In Central America *L. sibiricus* is called "marihuanilla" and used to replace marihuana.

Extracts of the aerial parts of several species were reported as heart antiarrhythmic,[69] sedative,[70] antibacterial,[71, 72] anticoagulant,[73] antioxidant,[74, 75] antitumoral,[76] booster of the immuno response.[77] The anticoagulant activity of *L. japonicus* was attributed[78] to hispanolone (**48**) and prehispanolone (**47**). Anti-oxidative stress effects on ischemic rat hearts was reported.[79]

In Bulgaria *Leonurus cardiaca* is used[33] against tachycardia, hypertonia and nervous disorders, while in Turkey is used[80] for the cardiotonic, expectorant, astringent and euphoric effects.

Table 1. *Leonotis* species content

Taxa	Compound	N° and Ref.
Leonotis leonurus	marrubiin	**1**[3]
	compound X	**2**[2, 4, 5]
	compound Y	**3**[2, 4, 6]
	premarrubiin (13*R*)	**4**[7]
	premarrubiin (13*S*)	**5**[7]
	leonurun	**22**[27]
Leonotis nepetaefolia	leonotin	**6**[8]
	nepetaefolin	**7**[11, 12, 13]
	nepetaefuran	**8**[12]
	nepetaefuranol	**9**[12]
	methoxynepetaefolin	**10**[14, 15]
	nepetaefolinol	**11**[15, 16, 17]
	leonotinin	**12**[16]
	dilactone	**13**[16]
	dehydronepetaefolinol	**14**[17]
	tetrol	**15**[17]
	leonotinic acid	**16**[18]
Leonotis dysophylla	leonotin	**6**[10]
Leonotis dubia	dubiin	**17**[19, 20]
Leonotis ocymifolia raineriana	leonotin	**18**[24]
	compound X	**2**[24]
	dilactone	**20**[24]
	lactone	**21**[24]
	leonotin	**6**[25]
	leonotinin	**12**[25]
	nepetaefolin	**7**[25]
Leonotis leonitis	leonitin	**18**[21, 22]
	leonotin	**6**[9]
Leonotis leonitis hirtiflora	diolide	**19**[23]

Table 2. *Leonurus* species content

Taxa	Compound	N° and Ref
Leonurus marrubiastrum	marrubiaside	**23**[29]
	marrubialactone	**25**[29]
	marrubiastrol	**26**[30]
	aldehydo-marrubialactone	**27**[30]
	desmethylmarrubiaketone	**28**[30]
	leonubiastrin	**36**[37]
Leonurus cardiaca	"clerodane B"	**29**[28, 31]
	leocardin	**30**[32]
	19-hydroxygaleopsin	**31**[33]
	19-acetoxypregaleopsin	**32**[34]
	leosibiricin	**35**[35]
Leonurus sibiricus	leosibirin	**33**[35]
	isoleosibirin	**34**[35]
	leosibiricin	**35**[35]
	sibiricinone A	**37**[38]
	sibiricinone B	**38**[38]
	sibiricinone C	**39**[38]
	sibiricinone D	**40**[38]
	sibiricinone E	**41**[38]
	15-*epi*-sibiricinone D	**42**[38]
	15-*epi*-sibiricinone E	**43**[38]
	compound LS-1	**44**[39]
	compound LS-2	**45**[39]
	leonotinin	**12**[39]
	leonotin	**6**[39]
	dubiin	**17**[39]
	nepetaefuran	**8**[39]
Leonurus heterophyllus	prehispanolone	**46**[40]
	hispanolone	**47**[43]
	leoheterin	**48**[43]
	preleoheterin	**49**[43]
	galeopsin	**50**[43]
	hispanone	**51**[44]
	leoheteronin A	**52**[44]
	leoheteronin B	**53**[44]
	leoheteronin C	**54**[44]

	leoheteronin D	**55**[44]
	leoheteronin E	**56**[44]
	heteronone A	**88**[55-57]
	heteronone B	**89**[56, 57]
Leonurus japonicus	preleoheterin	**49**[54]
	leojaponin	**85**[54]
	13-*epi*-preleoheterin	**86**[54]
	iso-preleoheterin	**87**[54]
Leonurus persicus	leopersin A	**57**[48]
	8-deacetoxyleopersin A	**58**[48]
	leopersin B	**59**[48]
	15-*epi*-leopersin B	**60**[48]
	19-hydroxypregaleopsin	**61**[48, 49]
	pregaleopsin	**62**[48]
	galeopsin	**50**[48]
	leosibiricin	**35**[48]
	leopersin C	**63**[49]
	15-*epi*-leopersin C	**64**[49]
	leopersin D	**65**[49]
	leopersin E	**66**[49]
	leopersin F	**67**[49]
	7-*epi*-leopersin F	**68**[49]
	leopersin G	**69**[50]
	leopersin H	**70**[50]
	leopersin I	**71**[50]
	leopersin J	**72**[50]
	15-*epi*-leopersin J	**73**[50]
	leopersin K	**74**[50]
	leopersin L	**75**[50]
	13-hydroxyballonigrinolide	**76**[50]
	ballotenol	**77**[50]
	leopersin M	**78**[53]
	leopersin N	**79**[53]
	leopersin O	**80**[53]
	15-*epi*-leopersin O	**81**[53]
	leopersin P	**82**[53]
	leopersin Q	**83**[53]
	15-*epi*-leopersin Q	**84**[53]
	19-hydroxygaleopsin	**31**[53]

Table 3. Diterpenes in *Leonotis* species

Compound	**Species**
marrubiin (**1**)	*leonurus*[3]
compound X (**2**)	*leonurus*,[2, 4, 5] *ocymifolia raineriana*[24]
compound Y (**3**)	*leonurus*[2, 4, 6]
13(*R*)-premarrubiin (**4**)	*leonurus*[7]
13(*S*)-premarrubiin (**5**)	*leonurus*[7]
leonotin (**6**)	*nepetaefolia*,[8] *leonitis*,[9] *dysophylla*,[10] *ocymifolia, raineriana*[25]
nepetaefolin (**7**)	*nepetaefolia*,[11, 12, 13] *ocymifolia raineriana*[25]
nepetaefuran (**8**)	*nepetaefolia*[12]
nepetaefuranol (**9**)	*nepetaefolia*[12]
methoxynepetaefolin (**10**)	*nepetaefolia*[14, 15]
nepetaefolinol (**11**)	*nepetaefolia*[15, 16]
leonotinin (**12**)	*nepetaefolia*,[16] *ocymifolia raineriana*[25]
dilactone (**13**)	*nepetaefolia*[16]
dehydronepetaefolinol (**14**)	*nepetaefolia*[17]
tetrol (**15**)	*nepetaefolia*[17]
leonotinic acid (**16**)	*nepetaefolia*[18]
dubiin (**17**)	*dubia*[19, 20]
leonitin (**18**)	*leonitis*,[21,22] *ocymifolia raineriana*[24]
diolide (**19**)	*leonitis hirtiflora*[23]
dilactone (**20**)	*ocymifolia raineriana*[24]
lactone (**21**)	*ocymifolia raineriana*[24]
leonurun (**22**)	*leonitis*[27]

Table 4. Diterpenes in the genus *Leonurus*

Compound	Species
leonotin (**6**)	*sibiricus*[39]
nepetaefuran (**8**)	*sibiricus*[39]
leonotinin (**12**)	*sibiricus*[39]
dubiin (**17**)	*sibiricus*[39]
marrubiaside (**23**)	*marrubiastrum*[29]
marrubialactone (**25**)	*marrubiastrum*[29]
marrubiastrol (**26**)	*marrubiastrum*[30]
aldehydomarrubialactone (**27**)	*marrubiastrum*[30]
desmethylmarrubiaketone (**28**)	*marrubiastrum*[30]
"clerodane B" (**29**)	*cardiaca*[31]
leocardin (**30**)	*cardiaca*[32]
19-hydroxy-galeopsin (**31**)	*cardiaca*,[33] *persicus*[53]
19-acetoxy-pregaleopsin (**32**)	*cardiaca*[34]
leosibirin (**33**)	*sibiricus*[35]
isoleosibirin (**34**)	*sibiricus*[35]
leosibiricin (**35**)	*cardiaca*,[36] *sibiricus*,[35] *persicus*[48]
leonubiastrin (**36**)	*marrubiastrum*[37]
sibiricinone A (**37**)	*sibiricus*[38]
sibiricinone B (**38**)	*sibiricus*[38]
sibiricinone C (**39**)	*sibiricus*[38]
sibiricinone D (**40**)	*sibiricus*[38]
sibiricinone E (**41**)	*sibiricus*[38]
15-*epi*-sibiricinone D (**42**)	*sibiricus*[38]
15-*epi*-sibiricinone E (**43**)	*sibiricus*[38]
compound LS-1 (**44**)	*sibiricus*[39]
compound LS-2 (**45**)	*sibiricus*[39]
prehispanolone (**46**)	*heterophyllus*[40]
hispanolone **47**)	*heterophyllus*[43]
leoheterin (**48**)	*heterophyllus*[43]
preleoheterin (**49**)	*heterophyllus*,[43] *japonicus*[54]
galeopsin (**50**)	*heterophyllus*,[43] *persicus*[48]
hispanone (**51**)	*heterophyllus*[44]
leoheteronin A (**52**)	*heterophyllus*[44]
leoheteronin B (**53**)	*heterophyllus*[44]
leoheteronin C (**54**)	*heterophyllus*[44]
leoheteronin D (**55**)	*heterophyllus*[44]
leoheteronin E (**56**)	*heterophyllus*[44]

leopersin A (**57**)	*persicus*[48]
8-deacetoxy-leopersin A (**58**)	*persicus*[48]
leopersin B (**59**)	*persicus*[48]
15-*epi*-leopersin B (**60**)	*persicus*[48]
19-hydroxypregaleopsin (**61**)	*persicus*[48, 49]
pregaleopsin (**62**)	*persicus*[48]
leopersin C (**63**)	*persicus*[49]
15-*epi*-leopersin C (**64**)	*persicus*[49]
leopersin D (**65**)	*persicus*[49]
leopersin E (**66**)	*persicus*[49]
leopersin F (**67**)	*persicus*[49]
7-*epi*-leopersin F (**68**)	*persicus*[49]
leopersin G (**69**)	*persicus*[50]
leopersin H (**70**)	*persicus*[50]
leopersin I (**71**)	*persicus*[50]
leopersin J (**72**)	*persicus*[50]
15-*epi*-leopersin J (**73**)	*persicus*[50]
leopersin K (**74**)	*persicus*[50]
leopersin L (**75**)	*persicus*[50]
13-hydroxyballonigrinolide (**76**)	*persicus*[50]
ballotenol (**77**)	*persicus*[50]
leopersin M (**78**)	*persicus*[53]
leopersin N (**79**)	*persicus*[53]
leopersin O (**80**)	*persicus*[53]
15-*epi*-leopersin O (**81**)	*persicus*[53]
leopersin P (**82**)	*persicus*[53]
leopersin Q (**83**)	*persicus*[53]
15-*epi*-leopersin Q (**84**)	*persicus*[53]
leojaponin (**85**)	*japonicus*[54]
13-*epi*-preleoheterin (**86**)	*japonicus*[54]
iso-preleoheterin (**87**)	*japonicus*[54]
heteronone A (**88**)	*heterophyllus*[55, 56, 57]
heteronone B (**89**)	*heterophyllus*[56, 57]

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